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(74) Agent: **MITCHARD, Leonard, C.**; Nixon & Vanderhye,
1100 North Glebe Road, Suite 800, Arlington, VA 22201-
4714 (US).

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(71) Applicant (*for all designated States except US*): **VIR-
GINIA COMMONWEALTH UNIVERSITY** [US/US];
1101 EAST Marshall Street Room 1-026, Richmond, VA
23298-0568 (US).

(72) Inventors; and

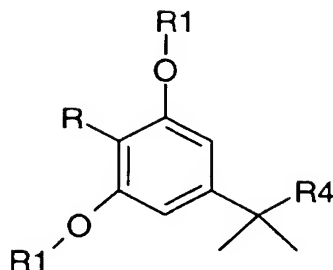
(75) Inventors/Applicants (*for US only*): **MARTIN, Billy, R.**
[US/US]; 2406 St. Regis Drive, Richmond, VA 23236
(US). **RAZDAN, Raj, K.** [US/US]; 34 Salt Island Road,
Gloucester, MA 01930 (US).

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(54) Title: CANNABINOIDS



(57) Abstract: Compounds of the formula: wherein R, R1 and R4 are defined in the specification, and pharmaceutically acceptable salts, esters and tautomers thereof, having activity at peripheral cannabinoid receptors, commonly designated the CB2 receptor class. The compounds are useful for therapy, especially in the treatment of pain, inflammation and autoimmune disease.

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CANNABINOIDS

BACKGROUND AND SUMMARY OF THE INVENTION

The present invention relates to novel compounds that have activity at peripheral cannabinoid receptors, commonly designated the CB2 receptor class. Particularly these compounds are more specific for said CB2 receptor class than many other compounds active on cannabinoid receptors CB1 and CB2.

At least five different classes of cannabinoids have been identified; traditional tricyclic tetrahydrocannabinoids, such as Δ^9 -tetrahydrocannabinoid (Δ^9 -THC), synthetic bicyclic cannabinoids such as CP55,940 (see Little et al (1988)), aminoalkylindole such as WIN55,212 (see D'Ambra et al (1992)), endocannabinoid such as anandamide (see Devane et al (1992)), and pyrazole antagonists such as SR141716A (see Rinaldi-Carmona (1994)). Although the chemical structure of these cannabinoids differ markedly, all of them contain at least one oxygen that is hypothesized to be involved in binding of these drugs to brain cannabinoid (CB1) receptors.

Δ^9 -THC, the primary psychoactive constituent of the marijuana plant, and other tetrahydrocannabinols contain two oxygens; a phenolic hydroxyl at position 1 and an oxygen pyran ring on the opposite side of the molecule. The hydroxyl oxygen interacts with the CB1 receptor through hydrogen bonding with a lysine residue (Lys 192) (see Song and Bonner (1996)). The role of the oxygen of the benzopyran substituent of Δ^9 -THC is less clear; however it is known that opening of the pyran ring as in CP55,940 does not eliminate binding or in vivo activity (See Little et al (1988)). In the absence of a phenolic hydroxyl, as in 1-deoxyanalogs of Δ^8 -THC, orientation of the cannabinoid molecule with respect to the CB1 receptor may be inverted and the pyran oxygen may substitute as a substrate for hydrogen bonding with Lys 192 (see Huffman et al (1996), (1999)).

In contrast to the high binding affinity of CP55,940 and other similar pyran-ring open analogs the natural product cannabidiol is also a pyran-ring open compound yet does not bind to CB1 or CB2 receptors nor does it have a cannabinoid profile of effects in vivo. Even the 1',1'-dimethylheptyl analog of cannabidiol binds very poorly to the CB1 receptor. With this in mind the present

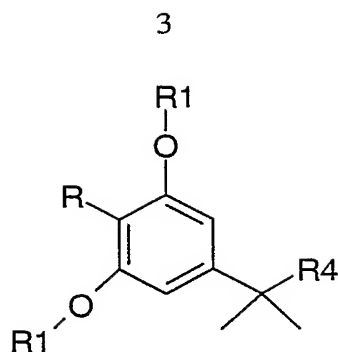
inventors have studied the structural activity relationship of resorcinol derivatives which could be considered as cannabidiol analogs.

During this study, Hanu et al (1999) published synthesis and activity of HU-3-8, a dimethoxyresorcinol derivative that is a CB2 selective agonist. The
5 transmembrane regions of CB2 receptors, which are involved in ligand recognition, exhibit 68% homology with those of CB1 receptors (see Munro et al (1993)). Showalter et al (1996) reported a high positive correlation ($r=0.82$) between binding affinities at these two cannabinoid receptors for cannabinoids in various classes; thus some of the structural features that enhance affinity for CB1 also
10 enhance affinity for CB2.

Addition of a 1',1'-dimethyl group to the lipophilic C3 side chain of Δ^8 -THC results in higher affinity for both receptors as compared to a nonbranched chain of identical length. Synthesis of a series of Δ^8 -THC analogs in which the phenolic hydroxyl at position 1 was removed (deoxy- Δ^8 -THC analogs) or was replaced with
15 a methoxyl resulted in analogs with selectivity for CB2 receptors (see Gareau et al (1996); Huffman et al (1996)(1999)). Incorporation of an oxygen into a fourth ring attached at C1 also increased CB2 selectivity, suggesting differences in the interaction of oxygen in the binding pockets of CB1 and CB2 (see Reggio et al (1997)).

20 The present inventors have now provided bicyclic resorcinols in which the core chemical structure contains two hydroxyl substituents positioned with a single intervening carbon in a benzene ring with a second cyclic substituent attached at the intermediate carbon.

In a first aspect of the present invention are provided novel compounds of
25 general formula I



wherein:

R is selected from the group consisting of optionally substituted carbocyclic and heterocyclic rings;

5 R1 is independently selected at each occurrence from the group consisting of hydrogen and C₁₋₆ alkyl;

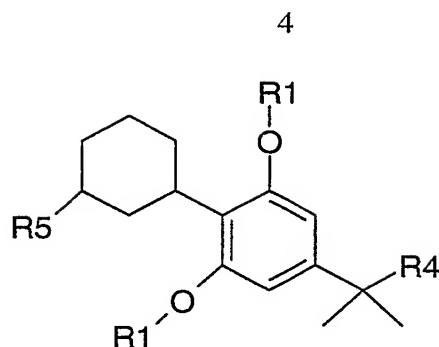
R4 is selected from the group consisting of C₁₋₁₀ alkyl or alkenyl; and pharmaceutically acceptable salts, esters and tautomers thereof.

10 Preferred compounds of the invention have R as optionally substituted aryl, e.g. phenyl, cyclohexyl, cycloheptyl, cyclohexenyl, cyclopentyl, tetrahydrothiopyranyl, methandienyl, cycloheptyl, adamantanyl, tetrahydrothiophen-3-yl, 1-alkyl-piperidinyl, 4-aryl-cyclohexyl, 3,3-dialkylcyclohexyl, tetrahydropyranyl, 1-cyclohexanolyl, 1-4-dioxospirocycloalkyl, and cyclohex-3-enonyl.

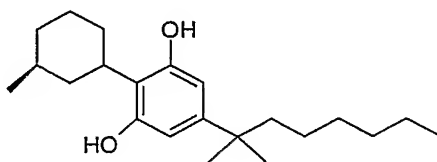
15 Preferred compounds of the invention have R1 as hydrogen or methyl.

Preferred compounds of the invention have R4 as linear C₅₋₇ alkyl, e.g., hexyl.

A preferred group of novel compounds of the first aspect of the invention are of general formula II



wherein R1 and R4 are as described for formula I and R5 is C₁₋₆ alkyl, more preferably methyl or ethyl. More preferably R1 is hydrogen or methyl, more preferably hydrogen. All isomers of compounds of formula II are of interest, but particularly preferred are isomer A and isomer B and the 3R-alkylcyclohexyl compounds, particularly compounds of formula



- 2-(3-methylcyclohexyl)-5-(1,1'-dimethylheptyl)-resorcinol isomer A (0-1797)
- 2-(3-methylcyclohexyl)-5-(1,1'-dimethylheptyl)-resorcinol isomer B (0-1798)
- 2-(3R-methylcyclohexyl)-5-(1,1'-dimethylheptyl)-resorcinol (0-1826).

A second aspect of the present invention provides a method of treating a patient in need of therapy for pain, particularly peripheral pain and/or inflammation or autoimmune disease comprising administering to that patient a therapeutically effective amount of a compound of formula I, more preferably of formula II. Such amount will typically be administered in a pharmaceutically acceptable carrier, such as is well known in the art.

A third aspect of the present invention provides a composition comprising a compound of formula I or II together with a pharmaceutically acceptable carrier and/or excipient. The composition should be sterile and, if intended for injection, non-pyrogenic.

Administration of the aforementioned compounds of the invention or a formulation thereof need not be restricted by route. Options include enteral (for example oral and rectal) or parenteral (for example delivery into the nose or lung or injection into the veins, arteries, brain, spine, bladder, peritoneum, muscles or subcutaneous region). The treatment may consist of a single dose or a plurality of doses over a period of time. The dosage will preferably be determined by the physician but may be between 0.01 mg and 1.0 g/kg/day, for example between 0.1 and 500 mg/kg/day. In terms of dose per square meter of body surface, the compound can be administered at 1.0 mg to 1.5 g per m² per day, for example 3.0-200.0 mg/m²/day.

Whilst it is possible for a compound of the invention to be administered alone, it is preferable to present it as a pharmaceutical formulation, together with one or more acceptable carriers and/or excipients. The carrier(s) and/or excipients must be "acceptable" in the sense of being compatible with the compound of the invention and not deleterious to the recipients thereof.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. A unit dosage form may comprise 2.0 mg to 2.0 g, for example 5.0 mg to 300.0 mg of active ingredient. Such methods include the step of bringing into association the active ingredient, i.e., the compound of the invention, with the carrier and/or excipients which constitute one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers and/or excipients and/or two or all of these, and then, if necessary, shaping the product.

Formulations in accordance with the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by

compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropyl-methyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycolate, PVP, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethylcellulose in varying proportions to provide desired release profile.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouth-washes comprising the active ingredient in a suitable liquid carrier.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which may render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

In a fourth aspect of the present invention there is provide a compound of the first aspect of the invention for use in therapy.

In a fifth aspect of the present invention there is provided the use of a compound of the first aspect of the invention for the manufacture of a medicament
5 for the treatment of a pain, inflammation and autoimmune disease.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will now be described further by reference to the following non-limiting examples and Figures. These are provided for the purpose of illustration only and other examples falling within the scope of the claims will occur to
10 those skilled in the art in the light of these. All literature references cited herein are incorporated by reference.

Figure 1 shows Chemical structures of Δ^9 -THC, CP 55,940, and cannabidiol;

Figure 2 shows a scheme for synthesis of resorcinol analogs;

15 Figure 3 shows scatterplots and regression lines of log CB₁ K_i plotted against log CB₂ K_i (top left panel) and log ED₅₀ for each of the three *in vivo* tests (SA = spontaneous activity, top right panel; MPE = % maximum possible antinociceptive effect, bottom left panel; RT = change in rectal temperature, bottom right panel); and

20 Figure 4 shows a cannabinoid receptor (CB₂) selective resorcinol derivative.

DETAILED DESCRIPTION OF THE INVENTION

Subjects

Male ICR mice (25-32g), obtained from Harlan (Dublin, VA), were housed in groups of five. All animals were kept in a temperature-controlled (20-22°C)
25 environment with a 12-hour light-dark cycle (lights on at 7 a.m.). Separate mice were used for testing each drug dose in the *in vivo* behavioral procedures. Brain tissue for binding studies was obtained from male Sprague-Dawley rats (150-200 g) purchased from Harlan Laboratories (Dublin, VA).

Apparatus

30 Measurement of spontaneous activity in mice occurred in standard activity chambers interfaced with a Digiscan Animal Activity Monitor (Omnitech Electronics, Inc., Columbus, OH). A standard tail-flick apparatus and a digital

thermometer (Fisher Scientific, Pittsburgh, PA) were used to measure antinociception and rectal temperature, respectively.

Compounds

Resorcinols were synthesized in our labs (Organix, Inc., Woburn, MA) according to the procedure specified below and were suspended in a vehicle of absolute ethanol, Emulphor-620 (Rhone-Poulenc, Inc., Princeton, NJ), and saline in a ratio of 1:1:18. Drugs were administered to the mice intravenously (i.v.) in the tail vein at a volume of 0.1 ml/10g.

Analog O-1376 and O-1532 listed in Table 1 were synthesized as previously described (Mahadevan et al., 2000). Analog O-1601 was synthesized from 1-deoxy-9-carbomethoxy cannabinol DMH analog (Mahadevan et al., 2000) by lithium/liquid ammonia reduction as described¹ for the preparation of O-1376. The compounds listed in Tables 2 and 3 were prepared using a three step sequence (Figure 1). The 2-lithio derivative of 1, 3-dimethoxy-5-(1', 1'-dimethylheptyl) resorcinol (**1**) was prepared using *n*-BuLi/hexane in THF. It was condensed with the appropriate ketone to give the tertiary alcohol **2**, which on treatment with trifluoroacetic acid/Et₃SiH gave the dimethoxy precursors **3**. Demethylation² with BBr₃/CH₂Cl₂ gave the target compounds (Crocker et al., 1999). The general procedure is illustrated in Figure 2 and described below.

To a solution of the resorcinol **1**, (5 mmol) in 25 ml of dry THF was added a 2.5 M solution of *n*-BuLi in hexane (5.5mmol) at 0 °C with stirring/N₂. After additional stirring for 1 h at 0 °C, added a solution of the ketone (7.5 mmol) in 3 ml of dry THF all at once. The solution was stirred for 0.5 h at 0 °C and then at 23 °C for 18 h. The reaction was worked up by the addition of sat NH₄Cl solution and extracted with ether. After washing (H₂O) and drying (Na₂SO₄) the solvent was evaporated to give the crude tertiary alcohol **2**, which was used as such in the subsequent reaction. A solution of the tertiary alcohol **2** (5 mmol) in 10 ml of dry CH₂Cl₂ was treated with CF₃COOH (27.5 mmol) followed by Et₃SiH (12.5 mmol). The solution was stirred/N₂ for 1 h or more (followed by TLC) and then quenched by the addition of sat NaHCO₃ solution. The organic layer was separated and after washing (H₂O) and drying gave the crude dimethoxy precursor **3** of the target compound. This material was used as such for the demethylation step. Treatment of **3**, as a solution in dry CH₂Cl₂ at 0 °C, with 3 equivalents of 1 N BBr₃ solution in

CH₂Cl₂, using the standard procedure and work up², gave the crude target compound, which was purified by chromatography, generally using hexane/ethyl acetate mixtures. In the case of O-1662 (Table 2), the corresponding tertiary alcohol **2** on treatment with CF₃COOH/ Et₃SiH gave the unsaturated compound (dehydrated but not reduced) which on catalytic reduction (PtO₂/C/H₂) in acetic acid gave the desired dimethoxy precursor **3**. The final compound was purified by chromatography using 5% Et₃NH₂/EtOAc mixture. The unsaturated analog O-1423 (Table 2) was prepared by treatment of the corresponding tertiary alcohol **2** with CF₃COOH alone in CH₂Cl₂ followed by demethylation. In Table 3, compounds O-1797-A and O-1798-B were diastereomeric mixtures and showed as two distinct spots in TLC which were separated by column chromatography, whereas O-1657 was a sample of the mixture of diastereomers O-1797-A and O-1798-B. The dimethoxy compounds listed in Tables 4 and 5 were prepared (Figure 2) from **1** and the appropriate ketones using BuLi, as in the preparation of **2**, and isolating and purifying the compounds by chromatography (ethyl acetate/hexane mixtures). Deprotection of O-2092 was carried out by treatment with 10% HCl in a ether/THF (5:4) mixture for 0.5 h at 23 °C to give a mixture of O-2115 (major) and the dehydrated compound O-2114 (minor). Sodium borohydride reduction of O-2115 furnished a mixture of diastereomeric compounds which were separated by chromatography to give the target compounds O-2116-A and O-2117-B. Similarly O-1966-A and O-1967-B were separated from a diastereomeric mixture by chromatography. Epoxidation of O-2114 followed by NaBH₄ reduction gave the target compound O-2122. In the preparation of O-2090 the corresponding diethoxy resorcinol derivative of **1** was used in place of **1**. All compounds showed appropriate ¹HNMRs (Jeol Eclipse 300 MHz) and were characterized on the basis of their ¹HNMRs, TLC, and elemental analyses.

Mouse Behavioral Procedures

Prior to testing in the behavioral procedures, mice were acclimated to the experimental setting (ambient temperature 22-24°C) overnight. Pre-injection control values were determined for rectal temperature and tail-flick latency (in sec). Five min after i.v. injection with drug or vehicle, mice were placed in individual activity chambers and spontaneous activity was measured for 10 min. Activity was

measured as total number of interruptions of 16 photocell beams per chamber during the 10-min test and expressed as % inhibition of activity of the vehicle group. Tail-flick latency was measured at 20 min post-injection. Maximum latency of 10 sec was used. Antinociception was calculated as percent of maximum possible effect $\{\%MPE = [(test - control\ latency) / (10 - control)] \times 100\}$. Control latencies typically ranged from 1.5 to 4.0 sec. At 30 min post-injection, rectal temperature was measured. This value was expressed as the difference between control temperature (before injection) and temperatures following drug administration ($^{\circ}C$). Different mice ($n=5-6$ per dose) were tested for each dose of each compound. Each mouse was tested in each of the 3 procedures.

CB₁ Binding Procedure

The methods used for tissue preparation and binding have been described previously (Compton et al., 1993) and are similar to those described by Devane et al. (1988). All assays, as described briefly below, were performed in triplicate, and the results represent the combined data from three to six individual experiments.

Following decapitation and rapid removal of the brain, whole brain was homogenized and centrifuged. The resulting pellet was termed P₁. The supernatant was saved and combined with the two subsequent supernatants obtained from washing of the P₁ pellet. The combined supernatant fractions were centrifuged, resulting in the P₂ pellet. After further incubation and centrifuging, this pellet was resuspended in assay buffer to a protein concentration of approximately 2 mg/ml. The membrane preparation was quickly frozen in a bath solution of dry ice and 2-methylbutane (Sigma Chemical Co., St. Louis, MO), then stored at $-80^{\circ}C$ for no more than 2 weeks. Prior to performing a binding assay an aliquot of frozen membrane was rapidly thawed and protein values determined by the method of Bradford (1976).

Binding was initiated by the addition of 150 μ g of P₂ membrane to test tubes containing 1 nM of [3H] CP 55,940 (79 Ci/mmol) and a sufficient quantity of buffer to bring the total incubation volume to 1 ml. Nonspecific binding was determined by the addition of 1 μ M unlabeled CP 55,940. Following incubation at $30^{\circ}C$ for 1 hr, binding was terminated by addition of ice cold buffer and vacuum filtration through pretreated filters in a 12-well sampling manifold (Millipore, Bedford, MA). After washing, filters were placed into plastic scintillation vials

(Packard, Downer Grove, IL) and shaken. The quantity of radioactivity present was determined by liquid scintillation spectrometry.

CB₂ Binding Procedure

Membranes for CB₂ binding were obtained from CHO cells. The transfected
5 cell line was maintained in Duplecco's Modified Eagle Medium (Gibco BRL, Grand Island, NY) with 10% fetal clone II (HyClone Laboratories, Inc., Logan, UT) plus 0.3 to 0.5 mg/ml G418 (to maintain selective pressure) under 5% CO₂ at 37°C. Cells were harvested with 1 mM EDTA in phosphate-buffered saline and were centrifuged at 1000 X g for 5 min at 4°C. The supernatant was saved and the P1
10 pellet was resuspended in centrifugation buffer. Homogenization and centrifugation were repeated twice and the combined supernatant fractions were centrifuged at 40,000 X g for 30 min at 4°C. The P2 pellet was resuspended in centrifugation buffer 2 (Tris HCl, 50 mM; EDTA, 1 mM; and MgCl₂, 3 mM, pH 7.4) to a protein concentration of approximately 2 mg/ml. Protein concentrations were
15 determined by the method of Bradford (1976) using Bio-Rad Protein Assay (Bio-Rad, Richmond, CA) and BSA standards (fatty acid free, Sigma Chemical Co., St. Louis, MO). The membrane preparation was divided into amounts convenient for binding assays and frozen rapidly in dry ice and stored at -80°C.

Binding was initiated by the addition of 50 • g of quickly thawed P2
20 membranes to test tubes containing [³H]CP-55,940 (final reaction concentration 0.5 nM), an appropriate concentration of unlabeled CP-55,940 or test drug, and sufficient quantity of assay buffer (50 mM Tris-HCl, 1 mM EDTA, 3 mM MgCl₂, 5 mg/ml bovine serum albumin, pH 7.4) to bring the total incubation volume to 0.5 ml. Concentration of [³H]CP-55,940 in saturation studies ranged from 50 to 10,000
25 pM. Nonspecific binding was determined by the addition of 1 • M unlabeled CP-55,940. CP-55,940 and all cannabinoid analogs were prepared by suspension in assay buffer from a 1 mg/ml ethanolic stock without evaporation of the ethanol (final concentration of no more than 0.4%). In competition studies, analog concentrations ranged from 0.1 nM to 10 • M. After incubation at 30°C for 1 hr,
30 binding was terminated by the addition of 2 ml of ice-cold wash buffer (50 mM Tris-HCl and 1 mg/ml BSA) and vacuum filtration through pre-treated filters in a 12-well sampling manifold (Millipore, Bedford, MA). Reaction vessels were washed once with 2 ml of ice-cold wash buffer. Filters were placed into 7-ml plastic scintillation

vials (RPI Corp., Mount Prospect, IL) with 4 ml of Budget-Solve (RPI Corp.). After shaking for 30 min, the radioactivity present was determined by liquid scintillation spectrometry. Three reaction vessels were used for each drug concentration in each assay. The results represent the combined data of three independent experiments. All assays were performed in siliconized test tubes, which were prepared by air drying (12 hr) inverted borosilicate tubes after two rinses with a 0.1% solution of AquaSil (Pierce, Rockford, IL). The GF/C glass-fiber filters (2.4 cm, Baxter, McGaw Park, IL) were pre-treated in a 0.1% solution of pH 7.4 polyethylenimine (Sigma Chemical Co.) for at least 6 hr.

10 Data Analysis

Based on data obtained from numerous previous studies with cannabinoids, maximal cannabinoid effects in each procedure were estimated as follows: 90% inhibition of spontaneous activity, 100% MPE in the tail flick procedure, and -6°C change in rectal temperature. ED₅₀'s were defined as the dose at which half maximal effect occurred. For drugs that produced one or more cannabinoid effect, ED₅₀'s were calculated separately using least-squares linear regression on the linear part of the dose-effect curve for each measure in the mouse tetrad, plotted against log₁₀ transformation of the dose. For the purposes of potency comparison, potencies were expressed as µmol/kg.

20 Pearson product-moment correlation coefficients (with associated significance tests) were calculated between CB₁ binding affinity (expressed as log K_i) and *in vivo* potency for each measure (expressed as log ED₅₀ in µmol/kg) for all active cannabinoid compounds that bound to the CB₁ receptor. In addition, multiple linear regression was used to calculate the overall degree of relationship between CB₁ binding affinity and potency in the mouse measures for all active cannabinoids. A correlation between CB₁ and CB₂ binding affinities was calculated for all compounds that had measurable K_i's for CB₁ and CB₂ binding (K_i < 10,000 nM). K_i values for CB₁ and CB₂ binding were obtained from Scatchard displacement analysis as determined via EBDA program of the KELL software package (Biosoft, Milltown, NJ).

The CB₁ and CB₂ binding affinities for substituted biphenyl analogs are shown in Table1. These compounds contain a phenolic hydroxyl and a lipophilic

side chain in the same orientation as in cannabinalol. In addition, the pyran oxygen is absent and the analogs have substituents in the phenyl ring (ring C) of cannabinalol. Two of the analogs (O-1376 and O-1601) have a dimethylheptyl side chain; each possessed good CB₁ and CB₂ binding affinities and in vivo activity. O-1601, the more potent of the two active compounds, had a hydroxymethyl group in the phenyl ring. This substitution increased CB₁ affinity and in vivo potencies compared to O-1376, but did not affect affinity for CB₂ receptors. A similar effect is observed in the cannabinalol series where the substitution of a hydroxymethyl group for a methyl at C-9 in cannabinalol increased binding affinity and potency (Mahadevan et al., 2000). Shortening the side chain of O-1376 to dimethylbutyl (O-1532) severely decreased affinity for both receptors and resulted in loss of in vivo activity.

Table 2 presents binding and in vivo data for a series of 2-cyclic ring substituted-5-dimethylheptyl resorcinols. Manipulation of the size of the cyclic structure attached at position 2 of the resorcinol ring resulted in changes in binding affinities and potencies. Substitution of a cyclopentane ring (O-1424) resulted in moderate affinity for the CB₁ receptor with excellent affinity for the CB₂ receptor. Although this compound was active in all three in vivo assays, potency was relatively poor. In addition, potencies across the measures were not equal; i.e., potency for reducing spontaneous activity was approximately half that for producing antinociceptive and hypothermic effects. Increasing ring size to a cyclohexane (O-1422), cycloheptane (O-1656), or adamantyl (O-1660) improved affinity 5- to 14-fold for both cannabinoid receptors and greatly increased potencies in vivo. Substitution of a sulfur for a carbon in a cyclohexane ring (O-1425) decreased CB₁ affinity by 14-fold and CB₂ affinity by 8-fold (compared to O-1422) as well as reducing in vivo potencies. Similarly, sulfur substitution in a cyclopentane ring (O-1661) also attenuated binding to both cannabinoid receptors. When a methylated nitrogen (O-1662) was inserted into the cyclohexane ring in

the same position as the sulfur of O-1425, binding to CB₁ receptors did not occur. In addition, CB₂ binding was drastically decreased and the compound was not fully active in vivo. In contrast, placing a double bond in the cyclohexane ring (O-1423) decreased affinities and potencies, but the compound remained active. However, moving the lipophilic side chain of O-1422 from C-5 to C-4 and replacing the DMH with a n-hexyl chain (O-2010) produced a 865-fold decrease in CB₁ affinity and a loss of activity in vivo.

Table 3 shows results of tests with cyclohexane substituted resorcinols in which the position of the substituent at the cyclohexane ring attached to the core resorcinol was varied. All compounds were diastereomeric mixtures. All of these analogs had good ($K_i = 2$ nM) to moderate ($K_i = 144$ nM) affinity for CB₁ receptors and were CB₂-selective (K_i range = 0.3 - 13 nM). Methylation at the 2 position of the cyclohexane ring (O-1658) did not dramatically alter affinity for either cannabinoid receptor or in vivo potencies compared to the corresponding cannabinoid with a non-methylated cyclohexane (O-1422 in Table 2). Moving the methyl to position 4 of the cyclohexane ring (O-1659) decreased affinity for both cannabinoid receptors by about 5-fold and produced an even greater decrease (11- to 24-fold) in potencies in vivo. Substituting a phenyl group for the methyl at this same position (O-1663) resulted in 2- to 3-fold decreases in CB₂ and CB₁ affinities, respectively, and a loss of activity in vivo. In the next five analogs shown in Table 3, the methyl was attached at position 3 of the cyclohexane ring. O-1657 exhibited CB₁ and CB₂ affinities that were similar to those of O-1658; however, the profiles of in vivo potencies differed. Whereas the two analogs showed approximately equal potencies in suppressing spontaneous activity, O-1658 was twice as potent in producing antinociception and three times as potent in reducing body temperature. By careful chromatography, compound O-1657 was separated into two distinct entities which were designated O-1797-A and O-1798-B. These analogs were still mixtures. Affinities of O-1797-A and O-1798-B were 2-3 times

greater than those of O-1657. While potencies of these isomers for suppression of locomotor activity and hypothermia were not notably different from those of O-1657, antinociceptive potencies were reduced by about half. The 3R isomer of this series (O-1826) showed decreased affinity for CB₁ receptors compared to O-1657; however, affinity for CB₂ receptors was identical for both compounds. Not surprisingly, given its decreased CB₁ affinity, O-1826 was less potent than O-1657 in vivo. Substitution of a dimethylbutyl for the DMH side chain at C5 of the resorcinol component (O-1890) decreased affinities for both cannabinoid receptors. This compound was active in vivo, although potency was notably low for all measures. In contrast, addition of a gem-dimethyl group at the 3 position of the cyclohexane ring with retention of the DMH side chain of the resorcinol component (O-1871) resulted in the best CB₁ and CB₂ affinities of this series. In vivo potencies, however, were lower than expected for this compound, given its higher CB₁ binding affinity.

In order to develop CB₂ selective ligands, we examined cyclic ring substituted dimethoxy resorcinols. The CB₁ and CB₂ binding affinities of these analogs are shown in Tables 4 and 5. Although most of the compounds shown in Tables 4 and 5 possessed a dimethylheptyl side chain, all had poor CB₁ affinity; hence, they were not tested in vivo. The bicyclic structure of O-1999 (Table 4) was almost identical to that of O-1657 (Table 3), an analog with good CB₁ and CB₂ affinities and potent in vivo effects. Both compounds had a dimethylheptyl side chain attached to the 5 position of a resorcinol core that was attached at position 2 to a cyclohexane ring. Each compound had a methyl group at the 3 position of the cyclohexane ring. The major structural difference between the two compounds was that O-1999 was a dimethoxy derivative of the resorcinol O-1657. This seemingly minor structural change from a phenol to a methoxy derivative resulted in complete loss of affinity for CB₁ receptors and an almost 600-fold reduction in affinity for CB₂ receptors. Similarly, the other analogs that were dimethoxy

derivatives of the corresponding resorcinols had poor affinity for CB₁ receptors (K_i ranged from 1716 to > 10,000), regardless of the cyclic ring substitution at position 2. In contrast, CB₂ binding affinities for some of these analogs remained high, as described in more detail below.

5 Table 4 presents binding data for 2-cyclic ring substituted dimethoxy-resorcinol-DMH analogs that contain at least one oxygen inserted into or attached to the non-resorcinol cyclohexane ring. Compared to O-1999 which did not contain an oxygen in the cyclohexane ring, conversion of the cyclohexane ring to a pyran ring (O-1964) decreased CB₂ affinity almost 2-fold without effect on CB₁
10 binding. Further addition of a double bond at position 3 of the pyran ring resulted in O-1965 which did not bind to either cannabinoid receptor. In contrast, the introduction of a tertiary hydroxyl group at C-4 of the pyran ring (O-1962) increased CB₂ affinity by 3-fold. Adding additional oxygens such as a ketol group attached at C-4 to the point of attachment of the dimethoxy resorcinol substituent (O-2092)
15 also increased CB₂ affinity whereas adding an oxygen as an epoxide (O-2122) decreased it. The presence of a ketone group at C-4 of the cyclohexane ring and having unsaturation in the ring (O-2114) resulted in a compound with poor affinity for either cannabinoid receptor; however, if a tertiary hydroxyl group was added at the site of dimethoxy resorcinol attachment (O-2115), CB₂ affinity improved.
20 Retention of the tertiary hydroxyl, methylation at position 5 and the presence of a ketone at position 3 of the cyclohexane ring increased affinity for both receptors and resulted in a compound (O-2123) with the best affinity (K_i = 125 nM) in this series.

 Table 5 shows CB₁ and CB₂ affinities for 2-cyclic ring substituted dimethoxy-resorcinol-DMH analogs in which the ring size and the position of the methyl or
25 hydroxyl substituent on the cyclohexane ring are varied. The first analog (O-2072) contains one hydroxyl attached to the cyclohexane at the same position at which the resorcinol core is attached. This compound is CB₂-selective. While it had poor

affinity for CB₁ receptors, it bound with moderate affinity to CB₂ receptors.

Introduction of a methyl substituent in the 3 position of the cyclohexane ring gave a diastereomeric mixture from which two distinct entities were separated by careful chromatography. These analogs (O-1966-A and O-1967-B) were still mixtures.

- 5 This substitution resulted in a 5-fold increase in affinity for CB₂ receptors with continued poor affinity for CB₁ receptors. However, one of these isomers (O-1966-A) showed the best CB₂ selectivity (225-fold) in the series and had high binding affinity for the CB₂ receptor ($K_i = 22.5$ nM). Addition of an extra hydroxyl group to the cyclohexane ring (O-2121) reduced both selectivity and binding affinity for the
- 10 CB₂ receptor comparable to those obtained with O-1967-B. Removal of the methyl at position 3 and addition of an hydroxyl at position 4 resulted in two diastereomeric mixtures which could be separated that were designated as O-2116-A and O-2117-B. Both of these isomers had poor affinity for CB₁ receptors, but while the B isomer also had poor affinity for CB₂ receptors, the A isomer bound
- 15 to CB₂ receptors with moderate affinity. Attachment of a gem-dimethyl group to position 3 of O-2072 (i.e., O-2068) did not significantly alter affinities for CB₁ or CB₂ receptors; however, replacement of the DMH group of O-2068 with a methyl group (O-2139) produced loss of affinity at both receptors. Changing the dimethoxy groups of the resorcinol by adding diethoxy groups (O-2090)
- 20 drastically decreased affinities for CB₁ and CB₂ receptors (compare O-2090 to O-1966-A or O-1967-B). Enlarging the cyclohexane ring in O-2072 to a cycloheptane ring(O-2091) resulted in little change in affinity for CB₁ receptors and an almost 2-fold increase in CB₂ affinity.

- As stated in the introduction, the lack of CB₁ binding affinity of cannabidiol
- 25 compared to other pyran-ring open analogs such as CP 55,940 prompted us to examine the structure-activity relationships of resorcinol derivatives for in vitro and in vivo cannabinoid activity. Our results show that many of the structural changes that affect CB₁ receptor recognition and activation in traditional bicyclic and tricyclic

cannabinoids similarly alter binding and activity in this resorcinol series. Previous research has shown that the length and branching of a lipophilic substituent is important for CB₁ receptor recognition in all of the major cannabinoid agonist classes, including tetrahydrocannabinols (Compton et al., 1993), bicyclic
5 cannabinoids (Compton et al., 1993), indole-derived cannabinoids (Wiley et al., 1998), and anandamides (Ryan et al., 1997; Seltzman et al., 1997). In the tricyclic and bicyclic series, a 1',1'-dimethylheptyl side chain is optimal (Compton et al., 1993) and is contained in most of the resorcinols presented here. Reducing the length of this substituent to 1',1'-dimethylbutyl (O-1532 and O-1890) or methyl (O-
10 2139) or a hydrogen (O-2010) resulted in a concomitant elimination or decrease in CB₁ receptor recognition, as occurs in other cannabinoid series with similar structural manipulations (see references above).

Other structural features affecting CB₁ receptor recognition and activation in this resorcinol series are related to the size, saturation, substitution, and
15 methylation of the second, non-resorcinol ring of these bicyclic cannabinoids. In most tricyclic and bicyclic cannabinoids, the ring corresponding to the non-resorcinol ring in the current series is a cyclohexane. Reducing this size to a cyclopentane decreases CB₁ affinity and potency whereas increasing it to a cycloheptane has little effect. Substitution of an adamantyl results in better CB₁
20 affinity; however, potency is decreased. Similar modifications of tricyclic and bicyclic cannabinoids have not been reported. The degree of saturation of the cyclohexane ring, however, has been manipulated in several cannabinoid classes. In the resorcinol series, the presence of a cyclohexane ring appeared optimal, although a thorough investigation of this issue was not undertaken. Introduction of
25 a single double bond (O-1423) within the ring decreased CB₁ affinity and potency to the same extent as did a reduction in the size of the ring to a cyclopentane. Hence, most structural manipulations were performed upon a bicyclic resorcinol-cyclohexane template. Degree of saturation of, as well as the position of the

double bond in the cyclohexane ring of tricyclic and bicyclic cannabinoids and in the polyolefin loop of the anandamides, has also been shown to affect CB₁ receptor recognition and activity in these cannabinoid classes. Greatest affinity and potency within the anandamides is achieved with four double bonds, with
5 greater or lesser saturation resulting in a reduction in CB₁ binding and/or in vivo activity (Adams et al., 1995; Sheskin et al., 1997; Thomas et al., 1996). Similarly, number and position of double bonds within the cyclohexane ring of tetrahydrocannabinols and bicyclic cannabinoids affect activity. For example, moving the double bond of Δ^9 -THC to position 8 (as in Δ^8 -THC) decreases CB₁
10 affinity three-fold and somewhat reduces potency (Compton et al., 1993). Unsaturation of the cyclohexane ring results in cannabinol with its greatly reduced CB₁ affinity (Showalter et al., 1996). In contrast, CP 55,940, with a completely saturated cyclohexane ring, is several fold more potent than Δ^8 -THC-DMH which has a single double bond in the cyclohexane ring, but Δ^8 -THC with its single
15 double bond binds with better CB₁ affinity than does $\Delta^{9(11)}$ -THC which has a completely saturated cyclohexane ring (Compton et al., 1993).

The most remarkable structural features of the resorcinol series affecting CB₁ affinity, however, are the length of the lipophilic side chain at position 5 and the size of the cyclic ring substituent at position 2 of the resorcinol core. THC and
20 CP 55,940 contain two oxygens: one as a phenol (one hydroxyl in the aromatic ring) with a second oxygen incorporated into a separate ring (pyran oxygen in THC) or a hydroxyl group attached as a substituent in the cyclohexane ring as in CP 55,940. Previous research has shown that eliminating the phenolic hydroxyl of Δ^8 -THC-like cannabinoids results in deoxy-THC analogs that are CB₂-selective
25 (Huffman et al., 1999). Although some of these deoxy-THC analogs also retain reasonable affinity for CB₁ receptors, orientation of their binding to CB₁ receptors may be inverted such that the pyran oxygen substitutes for the absent phenolic hydroxyl in hydrogen bonding (Huffman et al., 1996). In the absence of a pyran

oxygen, as in the resorcinols, the nature of the substituent at position 2 of the resorcinol core is important to maintain adequate CB₁ affinity for in vivo activity. An acyclic ring was found to be better than a heterocyclic ring with a cyclohexane ring being optimal for in vivo activity. In addition, the size and the position of the substituent on the cyclic ring is important to maintenance of CB₁ affinity. The presence of a methyl substituent at position 3 enhanced activity in some cases. Further, the 3R analog (O-1826; Table 2) has a poorer CB₁ binding affinity ($K_i = 40$ nM) compared to the diastereomeric mixture O-1657 ($K_i = 14$ nM; Table 2), suggesting that CB₁ binding affinity is enhanced when the orientation of the methyl substituent at position 3 in the cyclohexane ring is 3S compared to 3R. Methylation of the phenols of the resorcinols drastically decreased or eliminated CB₁ affinity, perhaps because hydrogen donation is less likely from a methoxy group than from THC's free hydroxyl group (B.R. Martin, unpublished observations). Similarly, methoxy substitution for the phenolic hydroxyl in the methyl esters of Δ^8 - and $\Delta^{9(11)}$ -THC-DMH resulted in analogs that were CB₂-selective and had little affinity for CB₁ receptors (Gareau et al., 1996; Huffman et al., 1999; Ross et al., 1999).

Notably, with the exception of a few compounds, the dimethoxyresorcinols tested here were CB₂-selective. Most of the structural features that affected recognition at CB₁ receptors also affected CB₂ receptor recognition, although not always to the same degree or in the same manner. These factors included length and branching of the side chain and size and degree of saturation of the non-resorcinol cyclohexane ring. In a SAR study on a series of CB₂-selective deoxy- Δ^8 -THC analogs, Huffman et al. (1999) reported that length and branching of the C3 side chain affected CB₂ binding in a manner similar to its effect on CB₁ affinity, as it did in the present study; however, the range of chain lengths for which moderate to good CB₂ affinity was retained for the deoxy- Δ^8 -THC analogs was greater than the range for CB₁ affinity. Similar results were obtained with a series

of CB₂-selective indole-derived cannabinoids in which length of the nitrogen substituent was varied (Aung et al., 2000). To date, anandamide analogs appear to be CB₁-selective with relatively little affinity for CB₂ receptors across several types of manipulations (Showalter et al., 1996). Insufficient research is available to
5 determine the effect of substitution on a cyclohexane ring on CB₂ affinity across cannabinoid classes.

Other structural manipulations eliminated or drastically reduced CB₁ receptor recognition, but did not necessarily alter CB₂ receptor binding in an identical manner. As mentioned, CB₂ selectivity was most evident in the
10 dimethoxy analogs, primarily as a consequence of severe reductions in CB₁ affinity. HU-308, the most selective CB₂ agonist to date, has a dimethoxy resorcinol core structure and does not bind to CB₁ receptors at all (Hanu_ et al., 1999). In addition, greater tolerance in CB₂ (vs. CB₁) receptor recognition was observed with other C2 substitutions in the resorcinols. Huffman et al. (2001)
15 recently reported that bicyclic pyridone analogs with carbonyl substitution at C1 and a nitrogen substituent substitution at C2 of THC had little affinity for CB₁ receptors. In contrast, moderate CB₂ affinity (K_i - 53 nM) was retained. Differences in allosteric regulation of CB₁ and CB₂ receptors by ions and guanine nucleotides has been noted previously (Showalter et al., 1996). Together, results
20 presented here and elsewhere (see above) suggest incomplete overlap of the pharmacophores for CB₁ and CB₂ receptors.

In summary, structure-activity relationships of the resorcinol series presented here are consistent with the CB₁ and CB₂ pharmacophores of other cannabinoid classes, including tetrahydrocannabinols, bicyclic cannabinoids,
25 aminoalkylindoles, and anandamides. In this series of resorcinols, several structural features were essential for maintenance of CB₁ receptor recognition and in vivo activity, including the presence of a branched lipophilic side chain (DMH) at C5, the presence of free phenols, and substitution of a cyclohexane ring at C2. An

important structural feature for receptor recognition at CB₂ receptors was side chain length, as reduction of the chain length to a methyl eliminated CB₂ binding affinity. The CB₂ selectivity observed with some resorcinols was maximized in the dimethoxyresorcinol analogs and this selectivity was greatly enhanced when a tertiary hydroxyl group was present in the cyclohexane ring in the same position at which the resorcinol core is attached. In contrast, the presence of unsaturation or a ketone group or an additional hydroxyl substitution in the cyclohexane ring adversely affected the CB₂ selectivity. Methyl ethers were optimal for CB₂ selectivity since ethyl ethers reduced selectivity.

In conclusion, although resorcinol derivatives with cyclic ring substituents at C2 are closely related to the nonactive cannabinoid cannabidiol, many of these analogs have high CB₁ and/or CB₂ binding affinity as well as potent in vivo activity. In addition, because dimethoxyresorcinols are CB₂ selective, they have potential to offer insight into similarities and differences between requirements for receptor recognition at CB₁ versus CB₂ receptors. One such difference noted here was the greater tolerance found for substitution at position 2, in the resorcinol series, for CB₂ receptor recognition compared to that for CB₁ receptors. The results presented here suggest that the resorcinol series represent a novel template for the development of CB₁ and CB₂ selective cannabinoid agonists.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not to be limited to the disclosed embodiment, but on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

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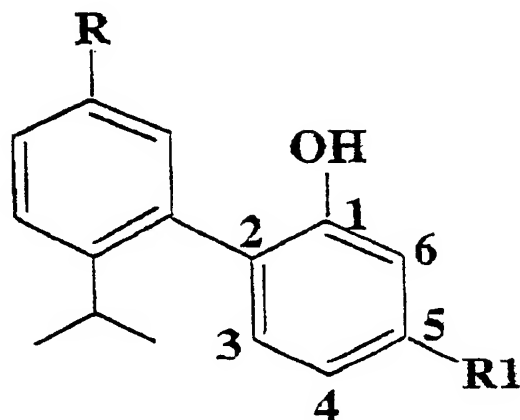
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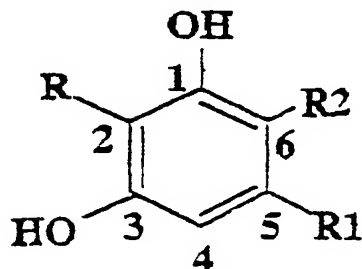
- 5 The disclosures of all of the above-cited references are incorporated herein by reference.

Table 1: CB_1 and CB_2 Binding Affinities and Pharmacological Effects of Phenols

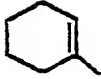

	ID	R	R1	K _i (nM)			ED ₅₀		
				CB ₁	CB ₂	CB ₁ /CB ₂	SA	TF	RT
1	O-1376	CH ₃	DMH	33 ± 4	3 ± 0.4	11	8.5 (5-16)	5.7 (3-10)	2.3 (1-5)
2	O-1532	CH ₃	DM-buryl	876 ± 18	113 ± 21	8	32% (30)	7% (30)	-0.4 (30)
3	O-1601	CH ₂ OH	DMH	5 ± 0.6	3 ± 0.4	2	1.1 (0.8-1.4)	1.1 (0.8-1.4)	1.6 (1.4-2.2)

The K_i 's are presented as means \pm SEM. All ED_{50} 's are expressed as $\mu\text{mol/kg}$ (with 95% confidence limits in parentheses). For compounds that failed to produce either maximal or dose-related effects, the percent effect at the highest dose (mg/kg; in parenthesis) is provided. SA = suppression of spontaneous activity; MPE = % maximum possible antinociceptive effect in tail flick assay; RT = rectal temperature. DMH=dimethylheptyl.

Table 2: Pharmacological Effects and Cannabinoid Receptor Binding Affinities of Bicyclic Resorcinols

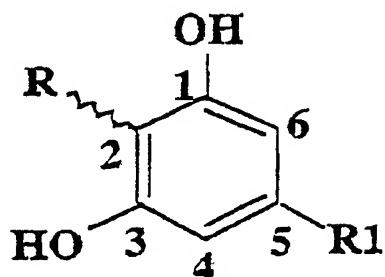


ID	R	R1	R2	K _i (nM)		CB ₁ /CB ₂	ED ₅₀		
				CB ₁	CB ₂		SA	TF	RT
O-1424		DMH	H	95 ± 6	7 ± 0.4	14	27 (13-56)	13 (9-23)	13 (10-20)
O-1422		DMH	H	11 ± 2	1.5 ± 0.1	7	0.1 (0.02-0.6)	0.6 (0.5-1.1)	0.6 (0.5-0.8)
O-1636		DMH	H	18 ± 1	2 ± 0.2	9	1.5 (0.4-7.0)	1.2 (0.9-1.5)	0.6 (0.1-8.0)
O-1660		DMH	H	7 ± 1	3 ± 0.8	2	3.5 (3.2-3.8)	2.4 (1.9-3.0)	4.6 (2.4-9.0)
O-1425		DMH	H	153 ± 17	12 ± 2	13	17 (10-29)	15 (10-24)	13 (10-19)
O-1661		DMH	H	138 ± 4	28 ± 12	5	24 (13-42)	14 (9-20)	24 (17-34)
O-1662		DMH	H	> 10,000	5424 ± 1103	—	87% (30)	30% (30)	-3 (30)

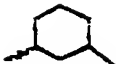
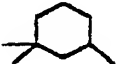
O-1423		DMH	H	97 ± 5	28 ± 5	3	12 (8-20)	9 (7-13)	9 (6-15)
O-2010		H	C_5H_{13}	9515 ± 332	NT	—	-18% (30)	9% (30)	-0.4 (30)

The K_i 's are presented as means \pm SEM. All ED_{50} 's are expressed as μ mol/kg (with 95% confidence limits in parentheses). For compounds that failed to produce either maximal or dose-related effects, the percent effect at the highest dose (mg/kg; in parenthesis) is provided. SA = suppression of spontaneous activity; MPE = % maximum possible antinociceptive effect in tail flick assay; RT = rectal temperature.

Table 3: *In Vitro and In Vivo Cannabinoid Effects of Bicyclic Resorcinols with Methylated Cyclohexane*

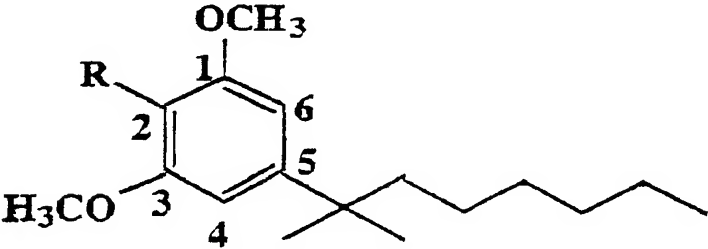












ID	R	R1	K _i (nM)		CB ₁ / CB ₂	ED ₅₀		
			CB ₁	CB ₂		SA	TF	RT
O-1658		DMH	16 ± 2	1 ± 0.3	16	0.2 (0.1-0.3)	0.3 (0.2-0.3)	0.3 (0.27-0.5)
O-1659		DMH	45 ± 1	5 ± 0.9	9	4.8 (3-9)	3.9 (3-6)	3.3 (2-5)
O-1663		DMH	144 ± 22	9 ± 2	16	32% (30)	7% (30)	-2.2 (30)
O-1657		DMH	14 ± 0.5	0.8 ± 0.04	17	0.3 (0.3-0.5)	0.6 (0.5-1)	0.9 (0.7-1.1)
O-1797A		DMH	5 ± 0.6	0.4 ± 0.03	12	0.5 (0.4-0.6)	1.1 (0.8-1.5)	0.7 (0.6-1.0)
O-1798B		DMH	4 ± 0.6	0.5 ± 0.07	8	0.2 (0.03-1.2)	1.0 (0.7-1.6)	0.6 (0.5-0.7)
O-1826		DMH	40 ± 11	0.8 ± 0.05	50	2.7 (2.1-3.9)	2.4 (1.8-3.3)	3.6 (2.7-4.5)

O-1890		DM- butyl	96 ± 4	13 ± 1	7	69 (55-90)	48 (31-69)	72 (45-114)
O-1871		DMH	2 ± 0.3	0.3 ± 0.01	7	< 1.0*	2.3 (2.0-2.6)	1.3 (0.3-4.3)

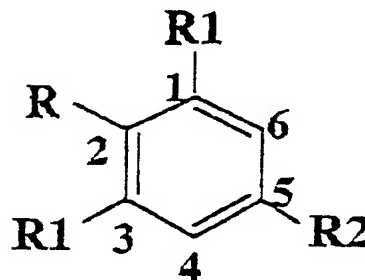
* This dose ($\mu\text{mol/kg}$) produced > 50% inhibition and was the lowest dose tested. The K_i 's are presented as means \pm SEM. All ED_{50} 's are expressed as $\mu\text{mol/kg}$ (with 95% confidence limits in parentheses). For compounds that failed to produce either maximal or dose-related effects, the percent effect at the highest dose (mg/kg ; in parenthesis) is provided. SA = suppression of spontaneous activity; MPE = % maximum possible antinociceptive effect in tail flick assay; RT = rectal temperature.

Table 4: CB₁ and CB₂ Binding Affinities of Dimethoxy-Dimethylheptyl Resorcinal Analogs

					
ID	CH ₂ OH	R	K _i (nM) ^a		
			CB ₁	CB ₂	CB ₁ /CB ₂
22	HU-308 ^a		> 10,000	23 ± 4	---
23	O-1999		>10,000	466 ± 110	---
24	O-1964		>10,000	911 ± 116	---
25	O-1965		>10,000	>10,000	---
26	O-1962		>10,000	342 ± 22	---
27	O-2092		4581 ± 312	126 ± 12	36
28	O-2122		3758 ± 184	1065 ± 107	4
29	O-2114		8442 ± 954	1773 ± 184	5
30	O-2115		4572 ± 173	346 ± 49	13
31	O-2123		1731 ± 117	125 ± 14	14

^b The K_i 's are presented as means \pm SEM.

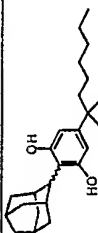
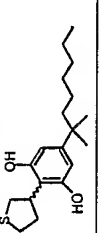
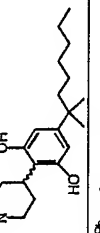
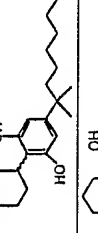
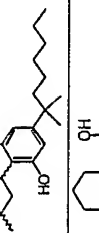
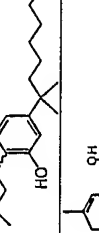
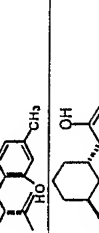
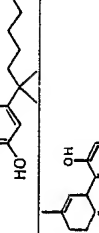
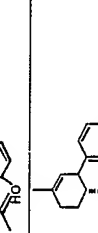
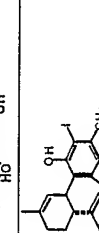
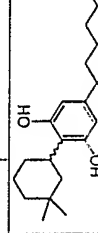
^a Values from Hanu_ et al., 1999. *Note:* Binding ligand, [³H]HU-243, was different from that used in present study.

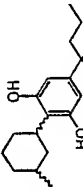
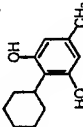
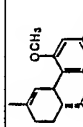
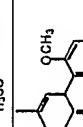
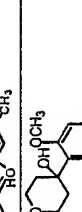
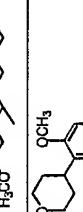
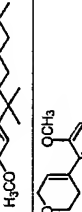
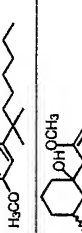
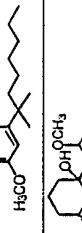
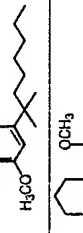
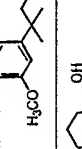
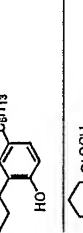
Table 5: CB_1 and CB_2 Binding Affinities of Hydroxylated Dimethoxy-Dimethylheptyl Resorcinols

ID	R	R1	R2	K _i (nM)		CB ₁ /CB ₂	
				CB ₁	CB ₂		
32	O-2072		OCH ₃	DMH	5820 ± 662	105 ± 19	55
33	O-1966A		OCH ₃	DMH	5055 ± 984	23 ± 2.1	220
34	O-1967B		OCH ₃	DMH	1716 ± 105	111 ± 8	15
35	O-2121		OCH ₃	DMH	1990 ± 77	101 ± 14	20
36	O-2116A		OCH ₃	DMH	3932 ± 483	190 ± 17	21
37	O-2117B		OCH ₃	DMH	>10,000	1561 ± 70	—
38	O-2068		OCH ₃	DMH	7515 ± 721	161 ± 24	47
39	O-2139		OCH ₃	CH ₃	>10,000	>10,000	—
40	O-2090		OC ₂ H ₅	DMH	8810 ± 422	858 ± 43	10
41	O-2091		OCH ₃	DMH	3201 ± 141	64 ± 8	50

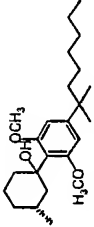
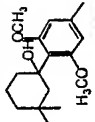
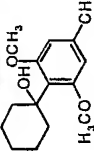
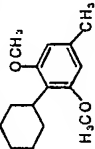
The K_i's are presented as means ± SEM.

A		C		D		I		J		K		L		M		N	
1	RAZDAN			STRUCTURE		CBI KI (nM)		CB2 KI (nM)		S.A.		T.F.		R.T.		Publication	
2	O#									ED50 (mg/kg) or % effect at dose							
3	O-1376	O-1376 = 3-1',1'-Dimethylheptyl-6-(2-isopropyl-5-methylphenyl)phenol				32.7±4.0	2.63±0.36	2.944	1.97	0.822	Wiley et al. (in press)						
4	O-1422	O-1422 = Cyclohexyl-5-(1',1'-dimethylheptyl)-resorcinol				11.33±2	1.46±0.1	0.3794	0.2412	0.19394	Wiley et al. (in press)						
5	O-1423	O-1423 = 2-(Cyclohex-1'-enyl)-5-(1',1'-dimethylheptyl)-resorcinol				96.65±5	27.62±5.13	3.918	2.856	2.944	Wiley et al. (in press)						
6	O-1424	O-1424 = 2-(Cyclopentyl)-dimethylheptyl-resorcinol				94.88±6	6.66±0.43	8.294	4.481	4.239	Wiley et al. (in press)						
7	O-1425	O-1425 = 2-(4'-Tetrahydrothiopyran-5-(1',1'-dimethylheptyl)-resorcinol				152.84±17	12.18±2.09	5.819	5.049	4.526	Wiley et al. (in press)						
8	O-1532	3-1',1'-Dimethylbutyl-6-(2-isopropyl-5-methylphenyl)-phenol				876±18.45	112.6±21				Wiley et al. (in press)						
9	O-1601	3-1',1'-Dimethylheptyl-6-(2-isopropyl-5-hydroxy-methylphenyl)-phenol				4.82±0.56	2.91±0.43				Wiley et al. (in press)						
10	O-1602	(-)-4-(3,4-trans-p-Menthadien-1,8)-yl-resorcinol				>10,000	>10,000	66% stim. @ 30	0 @ 30	0.3@30							
11	O-1656	2-Cycloheptyl-5-(1',1'-dimethylheptyl)-resorcinol				17.8±1.4	2.12±0.25	0.53	0.39	0.21	Wiley et al. (in press)						
12	O-1657	2-(3-Methylcyclohexyl)-5-(1',1'-dimethylheptyl)-resorcinol				14.4±0.53	0.82±0.04	0.13	0.23	0.29	Wiley et al. (in press)						
13	O-1658	2-(2-Methylcyclohexyl)-5-(1',1'-dimethylheptyl)-resorcinol				16.5±1.7	1.38±0.33	0.06	0.09	0.12	Wiley et al. (in press)						
14	O-1659	2-(4-Methylcyclohexyl)-5-(1',1'-dimethylheptyl)-resorcinol				45.22±1.52	4.73±0.94	1.65	1.35	1.12	Wiley et al. (in press)						

A		C	D	I	J	K	L	M	N
1	RAZDAN		STRUCTURE	CB1 KI (nM)	CB2 KI (nM)	S.A.	T.F.	R.T.	Publication
2	O#						ED50 (µg/kg) or % effect at dose		
15	O-1660	2-(2-Adamantanyl)-5-(1',1'-dimethylheptyl)-resorcinol		7.5±1.2	3.16±0.81	1.273	0.911	1.729	Wiley et al. (in press)
16	O-1661	2-(Tetrahydrothiophen-3-yl)-5-(1',1'-dimethylheptyl)-resorcinol		138±3.7	27.7±12.1	7.648	4.389	7.781	Wiley et al. (in press)
17	O-1662	2-(1-Methylpiperidin-4-yl)-5-(1',1'-dimethylheptyl)-resorcinol		>10,000	5424±1103	77% stim @ 10	7@ 10	1@ 10, Lethal @ 30	Wiley et al. (in press)
18	O-1663	2-(4-Phenylcyclohexyl)-5-(1',1'-dimethylheptyl)-resorcinol		143.7±21.9	8.8±1.6	32% @ 30	7% @ 30	neg.2.2' @ 30	Wiley et al. (in press)
19	O-1797	2-(3-Methylcyclohexyl)-5-(1',1'-dimethylheptyl)-resorcinol isomer A		5.21 ± 0.57	0.44±0.03	0.154	0.362	0.252	Wiley et al. (in press)
20	O-1798	2-(3-Methylcyclohexyl)-5-(1',1'-dimethylheptyl)-resorcinol isomer B		4.33 ± 0.58	0.48±0.07	0.070	0.379	0.218	Wiley et al. (in press)
21	O-1821	(1)-2-(3,3,4-trans-p-menthadien-(1,8)-yl)-orcinol		>10,000		0@ 30	8@ 30	neg 1 @ 30	
22	O-1826	2-(3R-Methylcyclohexyl)-5-(1',1'-dimethylheptyl)-resorcinol		40 ± 10.9	0.8 ± 0.05	0.915	0.821	1.162	Wiley et al. (in press)
23	O-1847	(1)-2-(3,3,4-trans-p-menthadien-(1,8)-yl)-resorcinol		>10,000					
24	O-1848	(1)-4-(3,3,4-trans-p-menthadien-(1,8)-yl)-resorcinol		>10,000					
25	O-1868	(1)-2-(3,3,4-trans-p-menthadien-(1,8)-yl)-4,6-dichloro-2,5-dimethylcyclohexyl-5-(1',1'-dimethylheptyl)-resorcinol		>10,000					
26	O-1871	2-(3,3-Dimethylcyclohexyl)-5-(1',1'-dimethylheptyl)-resorcinol		2.3±0.32	0.3±0.01	0.04	0.7	0.37	

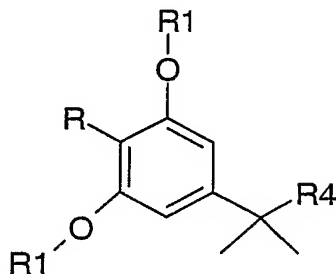
I	A	C	D STRUCTURE	J CBI KI (nM)	J CB2 KI (nM)	K S.A.	L T.F.	M R.T.	N Publication
2	O#					EL50 (ug/kg) or % effect at dose			
27	O-1890	2-(3-Methylcyclohexyl)-5-(1',1'-dimethylbutyl)-resorcinol		96.1 ± 3.53	13.2 ± 1.4	20	14	21	
28	O-1917	2-Cyclohexyl-5-methyl-resorcinol							
29	O-1918	(1'-1,3-Dimethoxy-2-(3-3,4-trans-p-menthadien-(1,8)-yl)-o-cinol							
30	O-1919	(1'-2-(3-3,4-trans-p-menthadien-(1,8)-yl)-monomethoxy o-cinol							
31	O-1962	O-1962 4-[4-(1,1-Dimethyl-heptyl)-2,6-dimethoxy-phenyl]-tetrahydropyran-4-ol		>10,000	342 ± 22.4	36% @ 30	23% @ 30	neg 0.9 @ 30	Wiley et al. (in press)
32	O-1964	O-1964 4-[4-(1,1-Dimethyl-heptyl)-2,6-dimethoxy-phenyl]-tetrahydro-pyran		>10,000	911 ± 116	neg 1.9 @ 30	30% @ 30	neg 0.6 @ 30	Wiley et al. (in press)
33	O-1965	O-1965 4-[4-(1,1-Dimethyl-heptyl)-2,6-dimethoxy-phenyl]-3,6-dihydro-2H-pyran		>10,000	>10,000				Wiley et al. (in press)
34	O-1966	O-1966 1-[4-(1,1-Dimethyl-heptyl)-2,6-dimethoxy-phenyl]-3-methyl-cyclohexanol isomer 1		5055 ± 983.8	23 ± 2.1	neg 19.0 @ 30	3.5 1 @ 30	0.5 @ 30	Wiley et al. (in press)
35	O-1967	O-1967 1-[4-(1,1-Dimethyl-heptyl)-2,6-dimethoxy-phenyl]-3-methyl-cyclohexanol isomer 2		1716.3 ± 104.8	111 ± 7.8	42.9 @ 30	8.2% @ 30	0 @ 30	Wiley et al. (in press)
36	O-1999	O-1999 5-(1,1-Dimethyl-heptyl)-1,3-dimethoxy-2-(3-methyl-cyclohexyl)-benzene		>10,000	465.6 ± 110	4 @ 30	6 @ 30	1 @ 30	Wiley et al. (in press)
37	O-2010	O-2010 2-Cyclohexyl-4-hexyl resorcinol		951.5 ± 332.5		neg 17.7% @ 30	9.0% @ 30	neg 0.4 @ 30	Wiley et al. (in press)
38	O-2068	O-2068 1-[4-(1,1-Dimethyl-heptyl)-2,6-dimethoxy-phenyl]-3,3-dimethyl-cyclohexanol		751.5 ± 720.9	161.48 ± 24.31				Wiley et al. (in press)

I RAZDAN	2 O#	A	C	D STRUCTURE	I CBI KI (nM)	J CB2 KI (nM)	K S.A. ED50 (ug/kg) or % effect at dose	L T.F.	M R.T.	N Publication
39	O-2072		O-2072 1-[4-(1,1-Dimethylheptyl)-2,6-dimethoxyphenyl]-cyclohexanol		5820.33±662.31	105.36±18.66				Wiley et al. (in press)
40	O-2090		O-2090 1-[4-(1,1-Dimethylheptyl)-2,6-diethylphenyl]-3-methyl cyclohexane-1-ol		8809.67±422.15	857.67±42.97				Wiley et al. (in press)
41	O-2091		O-2091 1-[4-(1,1-Dimethylheptyl)-2,6-dimethylphenyl]-cycloheptan-1-ol		3200.67±141.04	63.83±8.21				Wiley et al. (in press)
42	O-2092		O-2092 8-[4-(1,1-Dimethylheptyl)-2,6-dimethylphenyl]-1,4-dioxaspiro[4.5]decan-1-one		4581.33±311.65	125.53±12.45				Wiley et al. (in press)
43	2114		4-[4-(1,1-Dimethylheptyl)-2,6-dimethoxyphenyl]-4-hydroxycyclohexane		8441.7±954.3	1772.7±183.7				Wiley et al. (in press)
44	2115		1-[4-(1,1-Dimethylheptyl)-2,6-dimethoxyphenyl]-cyclohexane-1,4-diol (A)		4571.7±173.4	345.7±48.8				Wiley et al. (in press)
45	2116		1-[4-(1,1-Dimethylheptyl)-2,6-dimethoxyphenyl]-cyclohexane-1,4-diol (B)		3931.7±483.4	190.3±17.0				Wiley et al. (in press)
46	2117		Name of structure not given, also structure needs to be drawn. Presumably drawn with MW for C24H32O3, should be		>10,000	1561.3±69.7				Wiley et al. (in press)
47	2118		1-[4-(1,1-Dimethylheptyl)-2,6-dimethoxyphenyl]-5-methylcyclohexane-1,3-diol		6444.3±1389.5	3352±253.2				
48	2121		6-[4-(1,1-Dimethylheptyl)-2,6-dimethoxyphenyl]-7-oxabicyclo[4.1.0]heptan-3-ol		1990±76.66	100.67±13.88				Wiley et al. (in press)
49	2122		3-[4-(1,1-Dimethylheptyl)-2,6-dimethoxyphenyl]-3-hydroxy-5-methylcyclohexanone		3757.67±184.15	1065±107.08				Wiley et al. (in press)
50	2123				1730.67±116.86	124.93±14.40				Wiley et al. (in press)

1	A RAZDAN	C	D STRUCTURE	I CB1 KI (μ M)	J CB2 KI (μ M)	K S.A. ED50 (μ g/kg) or % effect at dose	L T.F.	M R.T.	N Publication
2	OW								
51	2137	O-2137 1-[4-(1,1-dimethyl-heptyl)-2,6-dimethoxy-phenyl]-3-methyl-cyclohexanol		2665 \pm 145.31	11.04 \pm 2.18				
52	2139	O-2139 1-[2,6-Dimethoxy-4-methyl-phenyl]-3,3-dimethyl-cyclohexanol		>10,000	>10,000				Wiley et al. (in press)
53	O-2298	1-[2,6-Dimethoxy-4-methyl-phenyl]-cyclohexanol		>10,000	>10,000				
54	O-2299	2-Cyclohexyl-1,3-dimethoxy-5-methylbenzene		>10,000	>10,000				

WHAT IS CLAIMED IS:

1. A compound of general formula I



5

wherein:

R is selected from the group consisting of optionally substituted carbocyclic and heterocyclic rings;

10 R1 is independently selected at each occurrence from the group consisting of hydrogen and C₁₋₆ alkyl;

R4 is selected from the group consisting of C₁₋₁₀ alkyl and alkenyl; and a pharmaceutically acceptable salt, ester and tautomer thereof.

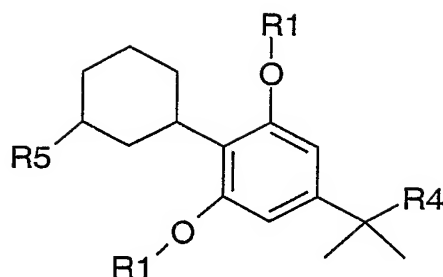
2. A compound as claimed in Claim 1 wherein R is optionally substituted aryl.

15 3. A compound as claimed in Claim 2 wherein said aryl is selected from the group consisting of phenyl, cyclohexyl, cycloheptyl, cyclohexenyl, cyclopentyl, tetrahydrothiopyranyl, methandienyl, cycloheptyl, adamantanyl, tetrahydrothiophen-3-yl, 1-alkyl-piperidiny, 4-aryl-cyclohexyl, 3,3-dialkylcyclohexyl, tetrahydropyranyl, 1-cyclohexanolyl, 1-4-dioxospirocycloalkyl and cyclohex-3-
20 enonyl.

4. A compound as claimed in Claim 1 wherein R1 is hydrogen or methyl.
5. A compound as claimed in Claim 1 wherein R4 is linear C₅₋₇ alkyl.
6. A compound as claimed in Claim 5, wherein R4 is hexyl.
7. A compound of general formula II:

25

42



wherein R1 is independently selected at each occurrence from the group consisting of hydrogen and C₁₋₆ alkyl;

R4 is selected from the group consisting of C₁₋₁₀ alkyl and alkenyl; and

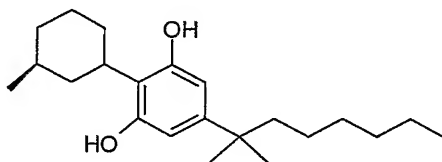
5 R5 is C₁₋₆ alkyl.

8. A compound as claimed in Claim 7, wherein R5 is methyl or ethyl.

9. A compound as claimed in Claim 7 wherein R1 is hydrogen or methyl.

10. A compound as claimed in Claim 7, wherein R1 is hydrogen.

10 11. A compound of the formula



12. A compound selected from the group consisting of:

2-(3-methylcyclohexyl)-5-(1,1'-dimethylheptyl)-resorcinol;

2-(3-methylcyclohexyl)-5-(1,1'-dimethylheptyl)-resorcinol; and

15 2-(3R-methylcyclohexyl)-5-(1,1'-dimethylheptyl)-resorcinol.

13. A composition comprising a compound of formula I, together with a pharmaceutically acceptable carrier and/or excipient.

14. A composition comprising a compound of formula II together with a pharmaceutically acceptable carrier and/or excipient.

20 15. A method of treating pain comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula I.

16. A method of treating pain comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula II.

17. A method as claimed in Claim 13, wherein said pain is peripheral pain.

5 18. a composition comprising a compound of formula I or II together with a pharmaceutically acceptable carrier and/or excipient. The composition should be sterile and, if intended for injection, non-pyrogenic

10 19. A method of treating inflammation comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula I.

20. A method of treating inflammation comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula II.

15 21. A method of treating autoimmune disease comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula I.

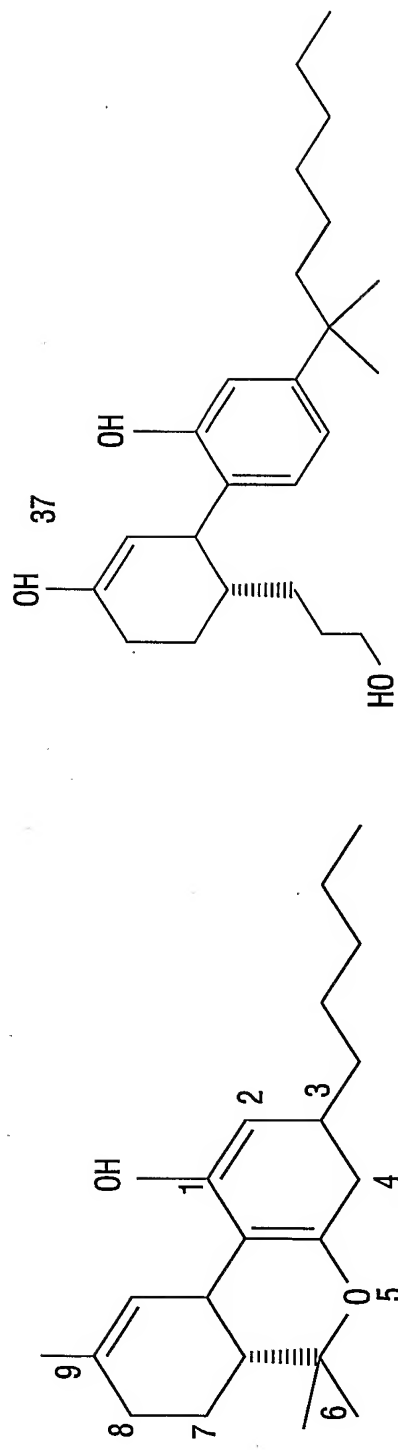
22. A method of treating autoimmune disease comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula II.

20 23. A compound of formula I for use in therapy.

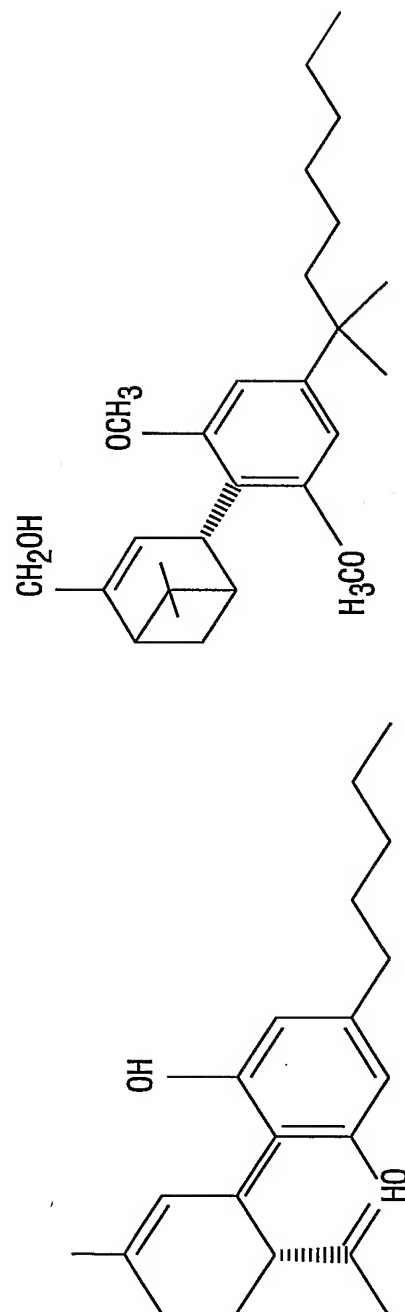
24. Use of a compound of formula 1 for the manufacture of a medicament for the treatment of a pain, inflammation and autoimmune disease.

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FIGURE 1

 Δ^9 -THC

CP 55,950



Cannabidiol

HU-308

FIGURE 2

(a) $n\text{-BuLi}$, hexane/THF, $0\text{ }^{\circ}\text{C}$, 1 h; ketone, THF, $0\text{ }^{\circ}\text{C}$, 0.5 h to $23\text{ }^{\circ}\text{C}$, 18 h, 80-90%; (b) CF_3COOH , Et_3SiH , CH_2Cl_2 , $23\text{ }^{\circ}\text{C}$, 1 h; (c) $\text{BBr}_3/\text{CH}_2\text{Cl}_2$, $0\text{ }^{\circ}\text{C}$ to $23\text{ }^{\circ}\text{C}$, 18 h; Overall yield (a to c), ~50-80%; (d) 10% HCl , ether/THF (5:4), $23\text{ }^{\circ}\text{C}$, 0.5 h; yield O-2115 (41%) and O-2114 (19%); (e) $m\text{-chloroperbenzoic acid}$, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (4:3), $23\text{ }^{\circ}\text{C}$, 10 min; (f) NaBH_4 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:1), $23\text{ }^{\circ}\text{C}$, 18 h, ~90%; Overall yield (e and f), ~50%.

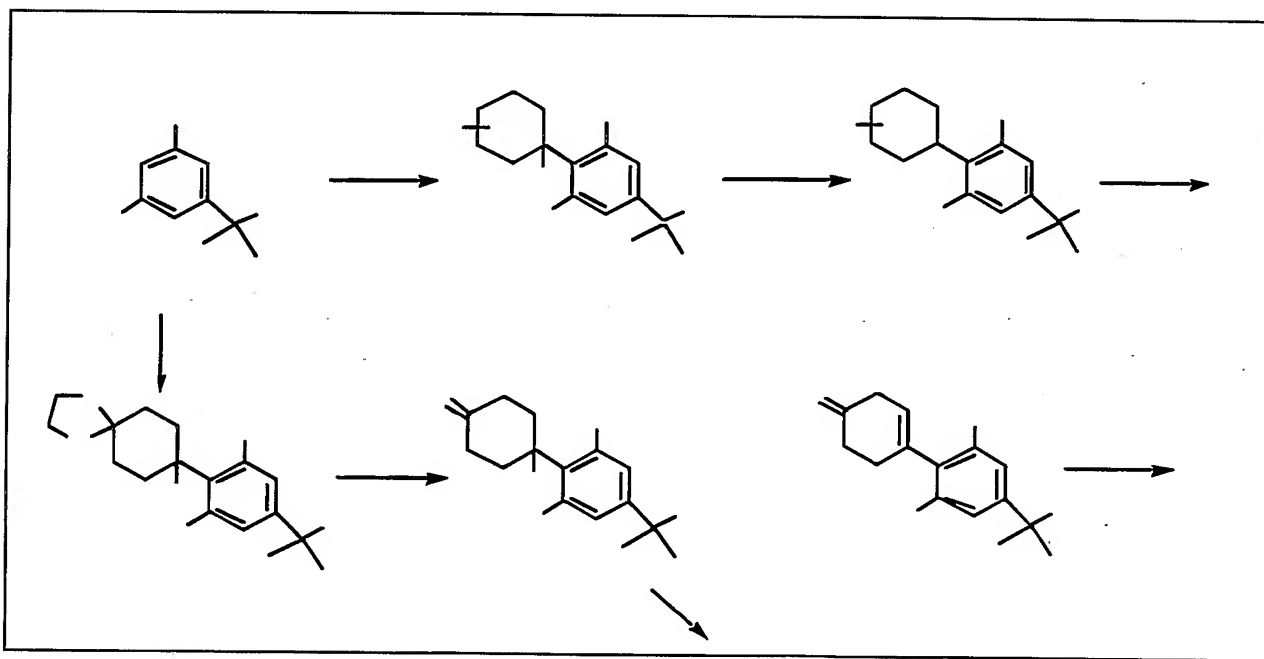


FIGURE 3

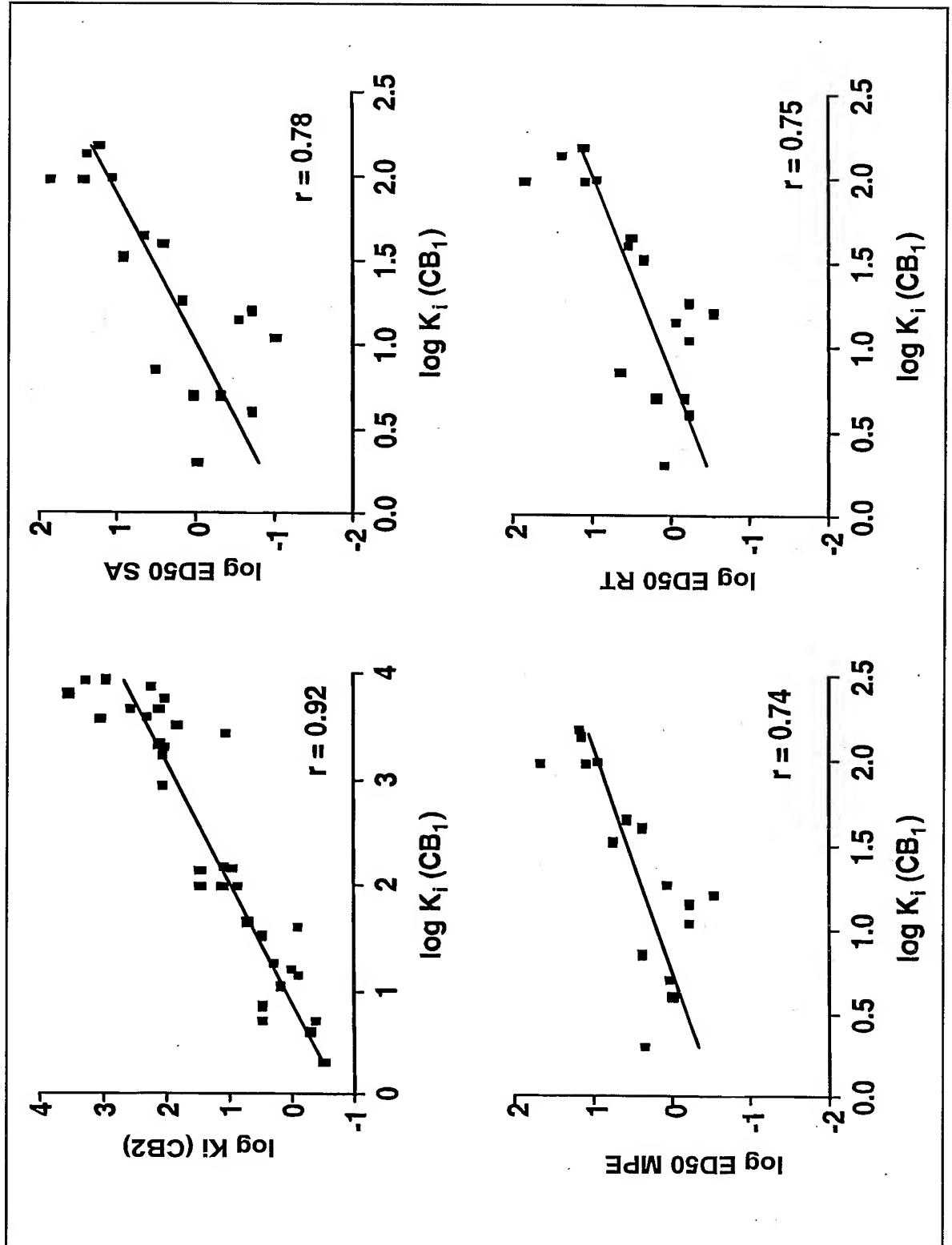
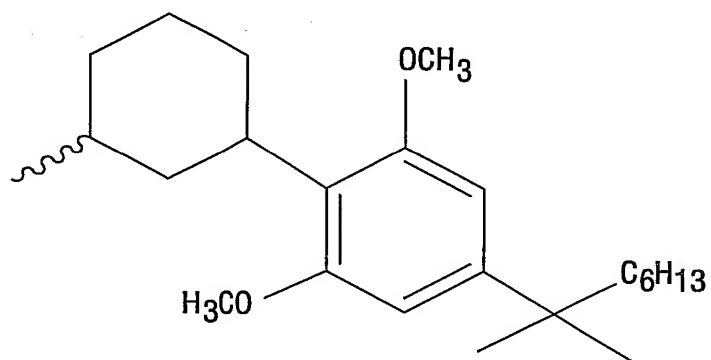


FIGURE 4

Cannabinoid Receptor (CB₂) Selective Resorcinol Derivative

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/19569

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C39/17 C07C43/23 C07C43/205 C07D333/08 C07D335/02
C07D309/10 C07D309/06 C07D211/22 A61K31/05 A61K31/09
A61K31/35 A61K31/4418 A61K31/381 A61P29/00 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US 4 707 559 A (MECHOULAM RAPHAEL ET AL) 17 November 1987 (1987-11-17) column 3, line 53 -column 5, line 65; examples IIIA,IVA,IA,IIID,IVD column 8; example IA; table I claims	1-6,13, 15, 17-19, 21,23,24
A	the whole document	1-24



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

3 December 2002

Date of mailing of the international search report

20/12/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bedel, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/19569

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X	US 4 282 248 A (MECHOULAM RAPHAEL ET AL) 4 August 1981 (1981-08-04) column 4; example XA; table I	1,2,13, 15, 17-19, 21,23,24
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A	page 192; examples 13,16; table 4 page 192, last paragraph	1-24
X	----- WO 01 028329 A (UNIVERSITY OF CONNECTICUT) 26 April 2001 (2001-04-26) page 8; figure 1; example 3	1,2
X	----- BAEK S-H ET AL: "BORON TRIFLUORIDE ETHERATE ON ALUMINA - A MODIFIED LEWIS ACID REAGENT. AN IMPROVED SYNTHESIS OF CANNABIDIOL" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 8, no. 26, 1985, pages 1083-1086, XP001095309 ISSN: 0040-4039 page 1084 -page 1085; examples 1B,12,14; table I	1,3
X	----- SEUNG-HWA BAEK: "BORON TRIFLUORIDE ETHERATE ON ALUMINA-A MODIFIED LEWIS ACID REAGENT..." BULL. KOREAN CHEM. SOC., vol. 15, no. 6, 1994, pages 507-508, XP002222551 left-hand column; figure 1 right-hand column; figure 2	1,3
X	----- US 4 092 344 A (MATSUMOTO KEN) 30 May 1978 (1978-05-30) examples ----- -/--	1,3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/19569

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BAEK, SEUNG-HWA: "Simplified cannabidiols. Part 1. Boron trifluoride-diethyl ether on alumina: a modified Lewis acid reagent. Friedel-Crafts alkylation of 5-alkylresorcinols with cyclic allylic alcohols" retrieved from STN Database accession no. 122:132675 XP002222552 abstract & SEUNG-HWA BAEK: J. CHEM. RESEARCH, 1994, pages 2549-2561, -----</p>	1,3
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X,P	<p>WO 01 95899 A (YISSUM RESEARCH DEVELOPPEMENT CO OF THE HEBREW UNIVERSITY OF JERUSALEM) 20 December 2001 (2001-12-20) claims; figures; examples -----</p>	1,3,13, 15, 17-19, 21,23,24

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Information on patent family members

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